We claim:

1. A method for identifying an effective agent that modulates a biological activity of a nuclear hormone receptor, comprising the steps of:

(a) contacting said nuclear hormone receptor with one or more agents and a eukaryotic cell sample to form a test sample under conditions suitable to form a receptor-containing complex;

(b) isolating said receptor-containing complex from said test sample;

(c) providing to said isolated receptor-containing complex conditions suitable for modification of said receptor-containing complex; and

(d) assaying said isolated receptor-containing complex for an altered modification state occurring in said isolated receptor-containing complex as compared to a control modification state,

wherein the presence of said altered modification state indicates that at least one of said one or more agents is an effective agent that modulates a biological activity of the nuclear hormone receptor.

2. A method for identifying an effective agent that modulates a biological activity of a nuclear hormone receptor, comprising the steps of:

(a) contacting said nuclear hormone receptor with one or more agents and a eukaryotic cell sample to form a test sample under conditions suitable to form a receptor-containing complex;

(b) isolating said receptor-containing complex from said test sample;

(c) providing to said isolated receptor-containing complex conditions suitable for phosphorylation of said receptor-containing complex; and

(d) assaying said isolated receptor-containing complex for an altered phosphorylation state occurring in said isolated receptor-containing complex as compared to a control phosphorylation state,

wherein the presence of said altered phosphorylation state indicates that at least one of said one or more agents is an effective agent that modulates a biological activity of the nuclear hormone receptor.

3. The method of claim 2, wherein said altered phosphorylation state is an increased phosphorylation state.

4. The method of claim 2, wherein said altered phosphorylation state is a decreased phosphorylation state.

5. A method for identifying an effective agent that modulates a biological activity of a nuclear hormone receptor, comprising the steps of:

(a) contacting said nuclear hormone receptor with one or more agents and a eukaryotic cell sample to form a test sample under conditions suitable to form a receptor-containing complex;

(b) isolating said receptor-containing complex from said test sample;

(c) providing to said isolated receptor-containing complex conditions suitable for phosphorylation of said receptor-containing complex; and

(d) assaying said isolated receptor-containing complex for an altered phosphorylation state occurring in said isolated receptor-containing complex as compared to a control phosphorylation state,

wherein said altered phosphorylation state is an altered phosphorylation state of said nuclear hormone receptor or an altered phosphorylation state of a 160 kDa protein, and

wherein the presence of said altered phosphorylation state indicates that at least one of said one or more agents is an effective agent that modulates a biological activity of the nuclear hormone receptor.

6. The method of claim 5, wherein said altered phosphorylation state is an altered phosphorylation state of said nuclear hormone receptor.

7. The method of claim 5, wherein said altered phosphorylation state is an altered phosphorylation state of a 160 kDa protein.

8. The method of claim 1, wherein said one or more agents are present during step (b).

9. The method of claim 2, where said conditions suitable for modification of said receptor-containing complex are a magnesium concentration of 1 to 25 mM.

10. The method of claim 1, wherein said nuclear hormone receptor is selected from the group consisting of a

retinoid X receptor (RXR),
hepatocyte nuclear factor 4 (HNF4),
testicular receptor,
tailless gene homolog (TLX),
Chicken ovalbumin upstream promoter transcription factor (COUP-TF),
thyroid receptor (TR),
retinoic acid receptor (RAR),

peroxisome proliferator activated receptor (PPAR),
reverse Erb (revErb),
RAR-related orphan receptor (ROR),
steroidogenic factor-1 (SF-1),
liver receptor homolog-1 (LRH-1),
liver X receptor (LXR),
farnesoid X receptor (FXR),
vitamin D receptor (VDR),
ecdysone receptor (EcR),
pregnane X receptor (PXR),
constitutive androstane receptor (CAR),
neuron-derived activated receptor (NOR1),
nuclear receptor related 1 (NURR1),
estrogen receptor (ER),
estrogen-related receptor (ERR),
glucocorticoid receptor (GR),
androgen receptor (AR),
progesterone receptor (PR) and
mineralocorticoid receptor (MR).

11. A method for identifying an effective agent that modulates a biological activity of a nuclear hormone receptor, comprising the steps of:

(a) contacting said nuclear hormone receptor with one or more agents and a eukaryotic cell sample to form a test sample under conditions suitable to form a receptor-containing complex,

wherein said nuclear hormone receptor is selected from the group consisting of a retinoid X

receptor, retinoic acid receptor, progesterone receptor, estrogen receptor, androgen receptor and vitamin D receptor;

(b) isolating said receptor-containing complex from said test sample;

(c) providing to said isolated receptor-containing complex conditions suitable for modification of said receptor-containing complex; and

(d) assaying said isolated receptor-containing complex for an altered modification state occurring in said isolated receptor-containing complex as compared to a control modification state,

wherein the presence of said altered modification state indicates that at least one of said one or more agents is an effective agent that modulates a biological activity of the nuclear hormone receptor.

12. The method of claim 11, wherein said nuclear hormone receptor is selected from the group consisting of RARα, RARβ, RARγ, RXRα, RXRβ and RXRγ.

13. The method of claim 11, wherein said nuclear hormone receptor is a retinoid X receptor (RXR) selected from the group consisting of RXRα, RXRβ and RXRγ.

14. A method for identifying an effective agent that modulates a biological activity of a retinoid X receptor, comprising the steps of:

(a) contacting said retinoid X receptor with one or more agents and a eukaryotic cell sample to form a test sample under conditions suitable to form a retinoid X receptor-containing complex;

(b) isolating said receptor-containing complex from said test sample;

(c) providing to said isolated receptor-containing complex conditions suitable for modification of said receptor-containing complex; and

(d) assaying said isolated receptor-containing complex for an altered phosphorylation state occurring in said isolated receptor-containing complex as compared to a control phosphorylation state,

wherein the presence of said altered modification state indicates that at least one of said one or more agents is an effective agent that modulates a biological activity of said retinoid X receptor.

15. The method of claim 1, wherein said nuclear hormone receptor is exogenous to said cell.

16. The method of claim 1, wherein said nuclear hormone receptor is truncated.

17. The method of claim 16, wherein said truncated nuclear hormone receptor lacks the native DNA-binding domain.

18. The method of claim 16, wherein said truncated nuclear hormone receptor consists essentially of the ligand-binding domain.

19. The method of claim 1, wherein said nuclear hormone receptor is a variant with an increased ratio of cytoplasmic to nuclear localization as compared to wild type nuclear hormone receptor.

20. The method of claim 1, wherein said nuclear hormone receptor is a variant that lacks a functional DNA-binding domain.

21. The method of claim 1, wherein said nuclear hormone receptor is a fusion protein comprising a heterologous membrane-anchoring domain.

22. The method of claim 1, wherein said nuclear hormone receptor is a fusion protein comprising a heterologous epitope tag.

23. The method of claim 1, wherein said nuclear hormone receptor is a fusion protein comprising a heterologous protein kinase recognition sequence.

24. The method of claim 1, wherein step (b) comprises specific binding to said receptor-containing complex.

25. The method of claim 24, wherein step (b) comprises immunoprecipitation of said receptor-containing complex.

26. The method of claim 25, wherein said immunoprecipitation is performed using antibody immunoreactive with said nuclear hormone receptor or a heterologous epitope fused thereto.

27. The method of claim 26, wherein said immunoprecipitation is performed using antibody immunoreactive with said nuclear hormone receptor.

28. The method of claim 2, wherein step (c) comprises incubating said receptor-containing complex with ATP.

29. The method of claim 1, wherein said test sample comprises an exogenous heterodimeric partner of said nuclear hormone receptor.

30. The method of claim 1, wherein said test sample comprises an exogenous kinase that enhances detection of said altered modification state.

31. The method of claim 1, wherein said eukaryotic cell sample comprises viable cells.

32. The method of claim 1, wherein said eukaryotic cell sample is a whole cell lysate.

33. The method of claim 1, wherein said eukaryotic cell sample is a fractionated cell lysate.

34. The method of claim 1, wherein said receptor-containing complex comprises a serine/threonine kinase.

35. A method for identifying an improved effective agent that modulates a biological activity of a nuclear hormone receptor, comprising the steps of:

(a) contacting said nuclear hormone receptor with one or more agents and a eukaryotic cell sample to form a test sample under conditions suitable to form a receptor-containing complex;

(b) isolating said receptor-containing complex from said test sample;

(c) providing to said isolated receptor-containing complex conditions suitable for modification of said receptor-containing complex,

(d) assaying said isolated receptor-containing complex for an altered modification state occurring in said isolated receptor-containing complex as compared to a control modification state; and

(e) assaying for direct transcriptional activity of said nuclear hormone receptor contacted with said one or more agents,

wherein the presence of said altered modification state combined with the absence of said direct transcriptional activity indicates that at least one of said one or more agents is an improved effective agent that modulates a biological activity of the nuclear hormone receptor.

36. A method for identifying an effective agent that modulates protein kinase A activity associated with a nuclear hormone receptor, comprising the steps of:

(a) contacting said nuclear hormone receptor with one or more agents and a cell sample to form a test sample under conditions suitable to form a receptor-containing complex;

(b) isolating said receptor-containing complex from said test sample;

(c) contacting said isolated receptor-containing complex with a protein kinase A substrate under conditions suitable for phosphorylation of said substrate; and

(d) assaying said substrate for an altered phosphorylation state as compared to a control phosphorylation state,

wherein the presence of said altered phosphorylation state indicates that at least one of said one or more agents is an effective agent that modulates protein kinase A activity associated with said nuclear hormone receptor.

37. The method of claim 36, wherein said altered phosphorylation state is an increased phosphorylation state.

38. The method of claim 36, wherein said altered phosphorylation state is a decreased phosphorylation state.

39. The method of claim 36, wherein said substrate is a purified substrate.

40. A method for identifying an effective agent that modulates protein kinase A activity associated with a nuclear hormone receptor, comprising the steps of:

(a) contacting said nuclear hormone receptor with one or more agents and a cell sample to form a test sample under conditions suitable to form a receptor-containing complex;

(b) isolating said receptor-containing complex from said test sample;

(c) contacting said isolated receptor-containing complex with a purified protein kinase A peptide substrate under conditions suitable for phosphorylation of said substrate; and

(d) assaying said peptide substrate for an altered phosphorylation state as compared to a control phosphorylation state,

wherein the presence of said altered phosphorylation state indicates that at least one of said one or more agents is an effective agent that modulates protein kinase A activity associated with said nuclear hormone receptor.

41. The method of claim 40, wherein said peptide substrate comprises a sequence selected from the group consisting of Arg-X-Ser, Arg-Arg-X-Ser, Arg-X-X-Ser, Lys-Arg-X-X-Ser and Arg-X-Lys-Arg-X-X-Ser-X (SEQ ID NO: 113), where X is independently any amino acid.

42. The method of claim 41, wherein said peptide substrate comprises the amino acid sequence Arg-X-Ser, where X is independently any amino acid.

43. The method of claim 42, wherein said peptide substrate comprises the amino acid sequence Arg-Arg-X-Ser, where X is independently any amino acid.

44. The method of claim 41, wherein said peptide substrate comprises the amino acid sequence Lys-Arg-X-X-Ser, where X is independently any amino acid.

45. The method of claim 44, wherein said peptide substrate comprises the amino acid sequence Arg-X-Lys-Arg-X-X-Ser-X (SEQ ID NO: 113), where X is independently any amino acid.

46. The method of claim 43, wherein said peptide substrate comprises an amino acid sequence selected from the group consisting of LRRASLG (SEQ ID NO: 59) and GRTGRRNSI (SEQ ID NO: 60).

47. The method of claim 40, 41, 42, 43, 44, 45 or 46, wherein said peptide substrate has at most ten residues.

48. The method of claim 39, wherein said purified substrate is myelin basic protein.

49. The method of claim 39, wherein said purified substrate has a Km of less than 20 μM for protein kinase A.

50. A method for identifying an effective agent that modulates protein kinase A activity associated with a nuclear hormone receptor, comprising the steps of:

(a) contacting said nuclear hormone receptor with one or more agents and a cell sample to form a test sample under conditions suitable to form a receptor-containing complex,

wherein said nuclear hormone receptor is selected from the group consisting of a retinoid X receptor (RXR), retinoic acid receptor (RAR) and a peroxisome proliferator activated receptor (PPAR);

(b) isolating said receptor-containing complex from said test sample;

(c) contacting said isolated receptor-containing complex with a protein kinase A substrate under conditions suitable for phosphorylation of said substrate; and

(d) assaying said substrate for an altered phosphorylation state as compared to a control phosphorylation state,

wherein the presence of said altered phosphorylation state indicates that at least one of said one or more agents is an effective agent that modulates protein kinase A activity associated with said nuclear hormone receptor.

51. The method of claim 50, wherein said nuclear hormone receptor is a retinoid X receptor (RXR).

52. The method of claim 51, wherein said retinoid X receptor is RXRα.

53. The method of claim 36, 51 or 52, wherein said nuclear hormone receptor is a variant with an increased ratio of cytoplasmic to nuclear localization as compared to wild type nuclear hormone receptor.

54. The method of claim 36, 51 or 52, wherein said nuclear hormone receptor is a fusion protein comprising a heterologous membrane-anchoring domain.

55. The method of claim 36, 51 or 52, wherein said nuclear hormone receptor is a fusion protein comprising a pleckstrin homology domain.

56. The method of claim 36, 51 or 52, wherein said nuclear hormone receptor is a fusion protein comprising a heterologous epitope tag.

57. The method of claim 36, 51 or 52, wherein said cell sample comprises an exogenous nucleic acid molecule encoding said nuclear hormone receptor.

58. The method of claim 36, 51 or 52, wherein said nuclear hormone receptor is endogenous to said cell sample.

59. The method of claim 36, 51 or 52, wherein said cell sample comprises an exogenous nucleic acid molecule encoding a heterodimeric partner of said nuclear hormone receptor.

60. The method of claim 36, 51 or 52, wherein said cell sample comprises an exogenous nucleic acid molecule encoding a catalytic subunit of protein kinase A.

61. The method of claim 36, wherein said cell sample comprises viable eukaryotic cells.

62. The method of claim 36, wherein said cell sample is a eukaryotic whole cell lysate.

63. The method of claim 36, wherein said one or more agents are present during step (b).

64. The method of claim 36, wherein step (b) comprises specific binding to said receptor-containing complex.

65. A method for identifying an effective agent that modulates protein kinase A activity associated with a nuclear hormone receptor, comprising the steps of:

(a) contacting said nuclear hormone receptor with one or more agents and a cell sample to form a test sample under conditions suitable to form a receptor-containing complex;

(b) immunoprecipitating said receptor-containing complex from said test sample, thereby isolating said receptor-containing complex;

(c) contacting said isolated receptor-containing complex with a protein kinase A substrate under conditions suitable for phosphorylation of said substrate; and

(d) assaying said substrate for an altered phosphorylation state as compared to a control phosphorylation state,

wherein the presence of said altered phosphorylation state indicates that at least one of said one or more agents is an effective agent that modulates protein kinase A activity associated with said nuclear hormone receptor.

66. The method of claim 65, wherein said immunoprecipitation is performed using antibody immunoreactive with said nuclear hormone receptor.

67. The method of claim 65, wherein said nuclear hormone receptor is a fusion protein comprising a heterologous epitope tag and said immunoprecipitation is performed using antibody immunoreactive with said epitope tag.

68. The method of claim 65, wherein step (d) comprises detecting radiolabeled substrate.